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*Institute Report No. 349*

**Primary Dermal Irritation Potential of  
Ball Powder® in Rabbits**

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*Larry D. Brown, DVM, LTC, VC  
and  
Don W. Korte, Jr., PhD, LTC, MSC*

MAMMALIAN TOXICOLOGY BRANCH  
DIVISION OF TOXICOLOGY

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Primary Dermal Irritation Potential of Ball Powder® in Rabbits (Toxicology Series 128)--  
Brown and Korte

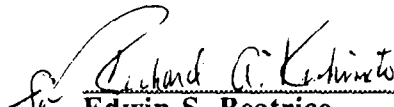
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Edwin S. Beatrice

COL, MC  
Commanding

11 July 1987  
(date)

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION / AVAILABILITY OF REPORT		
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE			APPROVED FOR PUBLIC RELEASE; DISTRIBUTION IS UNLIMITED.		
4. PERFORMING ORGANIZATION REPORT NUMBER(S)  Institute Report No.: 349			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION Mammalian Toxicology Division of Toxicology		6b. OFFICE SYMBOL (If applicable) SGRD-ULE-T	7a. NAME OF MONITORING ORGANIZATION US Army Biomedical Research and Development Laboratory		
6c. ADDRESS (City, State, and ZIP Code) Letterman Army Institute of Research Presidio of San Francisco, CA 94129-6800		7b. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21701-5010			
8a. NAME OF FUNDING / SPONSORING ORGANIZATION US Army Medical Research & Development Command		8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER		
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5012		10. SOURCE OF FUNDING NUMBERS	PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.
			62720	A835	AB
					DA303913
11. TITLE (Include Security Classification) (U) Primary Dermal Irritation Potential of Ball Powder® in Rabbits					
12. PERSONAL AUTHOR(S) LD Brown and DW Korte, Jr.					
13a. TYPE OF REPORT Institute		13b. TIME COVERED FROM 24 JAN 85 TO 27 FEB 85		14. DATE OF REPORT (Year, Month, Day) July 1989	
				15. PAGE COUNT 15	
16. SUPPLEMENTARY NOTATION  Toxicology Series No. 128					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	Primary Dermal Irritation, Ball Powder®, Rabbit, Mammalian Toxicology, Propellant		
19. ABSTRACT (Continue on reverse if necessary and identify by block number) The primary dermal irritation potential of Ball Powder® was determined in 4 male and 4 female New Zealand White rabbits by using a modified Draize method. Two Ball Powder® skin application sites were evaluated on each animal following a 4-hour application to closely clipped skin. Very slight erythema was observed in 1 rabbit at 1 hour after wrap removal and in 2 rabbits at 24 hours after wrap removal. All rabbits had returned to normal by 48 hours after dosing. Neither edema nor any other recognizable skin reaction was detected at any time during the 14-day observation period. Ball Powder® was classified as a non-irritant under conditions of this study.					
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT <input checked="" type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED		
22a. NAME OF RESPONSIBLE INDIVIDUAL EDWIN S. BEATRICE, COL, MC			22b. TELEPHONE (Include Area Code) (415) 561-3600		22c. OFFICE SYMBOL SGRD-ULZ

## ABSTRACT

The primary dermal irritation potential of Ball Powder® was determined in 4 male and 4 female New Zealand White rabbits by using a modified Draize method. Two Ball Powder® skin application sites were evaluated on each animal following a 4-hour application to closely clipped skin. Very slight erythema was observed in 1 rabbit at 1 hour after wrap removal and in 2 rabbits at 24 hours after wrap removal. All rabbits had returned to normal by 48 hours after dosing. Neither edema nor any other recognizable skin reaction was detected at any time during the 14-day observation period. Ball Powder® was classified as a non-irritant under conditions of this study.

KEY WORDS: Primary Dermal Irritation, Ball Powder®, Propellant, Mammalian Toxicology, Rabbit

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## **PREFACE**

**TYPE REPORT:** Primary Dermal Irritation GLP Study Report

**TESTING FACILITY:**

US Army Medical Research and Development Command  
Letterman Army Institute of Research  
Presidio of San Francisco, CA 94129-6800

**SPONSOR:**

US Army Medical Research and Development Command  
US Army Biomedical Research and Development Laboratory  
Fort Detrick, MD 21701-5010  
Project Officer: Gunda Reddy, PhD

**PROJECT/WORK UNIT/APC:** 3E162720A835/180/TLBO

**GLP STUDY NUMBER:** 84033

**STUDY DIRECTOR:** LTC Don W. Korte, Jr., PhD, MSC  
Diplomate, American Board of Toxicology

**PRINCIPAL INVESTIGATOR:** LTC Larry D. Brown, DVM, VC  
Diplomate, American College of Veterinary  
Preventive Medicine, American Board of Toxicology

**PATHOLOGIST:** LTC Lance O. Lollini, DVM, VC  
Diplomate, American College of Veterinary Pathologists

**REPORT AND DATA MANAGEMENT:**

A copy of the final report, study protocol, retired SOPs, raw data, analytical, stability, and purity data of the test compound, and an aliquot of the test compound will be retained in the LAIR Archives.

**TEST SUBSTANCE:** Ball Powder®

**INCLUSIVE STUDY DATES:** 24 January - 27 February 1985

**OBJECTIVE:** The objective of this study was to determine the primary dermal irritation potential of Ball Powder® in male and female New Zealand White rabbits.

## **ACKNOWLEDGMENTS**

SP4 John R.G. Ryabik, BS, assisted in the research; SP4 James J. Fisher, SP4 Scott L. Schwebe, Richard A. Spieler, and Charlotte Speckman provided care for the animals; and Colleen S. Kamiyama, Dorothy Davis, and Dianna Johnson provided secretarial assistance.

## SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 84033 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte, Jr. 11 July 89

DON W. KORTE, JR., PhD / DATE  
LTC, MS  
Study Director

Larry D. Brown 13 July 1987

LARRY D. BROWN, DVM / DATE  
LTC, VC  
Principal Investigator

Conrad Wheeler 10 July 89

CONRAD WHEELER, PhD / DATE  
DAC  
Analytical Chemist



DEPARTMENT OF THE ARMY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129-6800

REPLY TO  
ATTENTION OF:

SGRD-ULZ-QA

5 July 1989

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 84033

1. This is to certify that the protocol for LAIR GLP Study 84033 was reviewed on 1 November 1984.
2. The institute report entitled "Primary Dermal Irritation Potential of Ball Powder in Rabbits," Toxicology Series 128, was audited on 23 July 1987.

*Carolyn M. Lewis*

CAROLYN M. LEWIS, MS  
Diplomate, American Board of  
Toxicology  
Quality Assurance Auditor



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## **Primary Dermal Irritation Potential of Ball Powder® in Male and Female Rabbits—Brown and Korte**

### **INTRODUCTION**

Nitroguanidine, a primary component of US Army triple-base propellants, is now produced in a Government-owned contractor-operated ammunition plant. The US Army Biomedical Research and Development Laboratory (USABRDL), as part of its mission to evaluate the environmental and health hazards of military-unique propellants generated by US Army munitions-manufacturing facilities, conducted a review of the nitroguanidine data base and identified significant gaps in the toxicity data (1). The Division of Toxicology, LAIR, was tasked by USABRDL to develop a genetic and mammalian toxicity profile for nitroguanidine, related intermediates/by-products of its manufacture, and its environmental degradation products. A genetic and acute mammalian toxicity profile of Ball Powder®, a fielded nitrocellulose-based propellant, was also requested as a baseline against which future formulations will be compared.

#### Objective of Study

The objective of this study was to determine the primary dermal irritation potential of Ball Powder® in male and female New Zealand White rabbits.

### **MATERIALS**

#### Test Substance

Name: Ball Powder® (Olin WC 844 double base spheroidal propellant)

LAIR Code Number: TA45

Chemical Composition:

<u>Component</u>	<u>Percent</u>
Nitroglycerin	10.235
Dinitrotoluene	0.685
Diphenylamine	1.105
Dibutylphthalate	5.255
Nitrocellulose	83.23
Total Volatiles	1.045
Moisture and Volatiles	0.895
Residual Solvent	0.49
Calcium Carbonate	0.09
Sodium Sulfate	0.12

Source: Badger Army Ammunition Plant  
Baraboo, WI 53913

Other test substance information is presented in Appendix A.

Vehicle

Viaflex® sterile isotonic saline (Travenol Laboratories, Deerfield, IL) was used as the vehicle for Ball Powder®. The expiration date for the saline (lot 7C950X0) used in this study was Oct 85.

Animal Data

Four male and four female New Zealand White rabbits (Elkhorn Rabbitry, 5265 Starr Way, Watsonville, CA), identified individually with ear tattoos numbered 85F018 to 85F021 (females) and 85F022-85F025 (males) inclusive, were assigned to the study. The animal weights on dosing day (13 Feb 85) ranged from 3.41 to 4.25 kg. Additional animal data appear in Appendix B.

Husbandry

The rabbits were housed individually in stainless steel, screen-bottomed, battery-type cages with automatically flushing dump tanks. The diet consisted of 150 g per day of Certified Purina Chow® Diet 5322 (Ralston Purina Company, Checkerboard Square, St. Louis, MO); water was provided by continuous drip from a central line. The animal room temperature was

maintained at 15.5° to 20.5°C with a relative humidity range of 39% to 63% with short spikes up to 70% associated with room cleaning. The photoperiod was 12 hours of light per day.

## **METHODS**

### Group Assignment/Acclimation

Study animals were acclimated for 5 days to the study room following a 14-day quarantine by the Division of Animal Care and Services (DACS). During this period they were observed daily for signs of illness. They were treated prophylactically for ear mites with a single dose of Canex® and mineral oil instilled in the ears.

### Test Procedures

This study was conducted in accordance with EPA guidelines (2) and LAIR SOP-OP-STX-34 (3).

The backs of 8 rabbits were close-clipped 24 hours before the actual dosing. The clipped area was divided into 4 quadrants designated I-IV (4, 5). Site I was designated a sham patch site. Sites II and III were test compound sites. Site IV was a saline control patch site. A standard dose of 0.5 g of Ball Powder® was moistened with enough (usually 0.5 ml) 0.9% sodium chloride solution to make a thick paste. This paste was placed on 1-inch (2.5 cm) square gauze patch that was taped to the appropriate site. Blenderm® (Medical Products Division of 3M, Saint Paul, MN), an occlusive, hypoallergenic surgical tape, was used to hold the patches in place. Vet Wrap® (Animal Care Products Division of 3M, Saint Paul, MN) was then wrapped securely around the animal and taped down with Conform® elastic tape (Kendall Company, Boston, MA). The test compound was left in contact with the skin for 4 hours. At the end of the exposure period the wrapping and patches were removed, and the skin was gently wiped with a saline-moistened gauze to remove any test material remaining on the skin.

Observations

The grading and scoring for dermal reactions were performed according to Table 1. Scoring and grading for dermal irritation were performed at 30-60 minutes and approximately 24, 48, and 72 hours after removal of the patch. Observations for clinical signs were made daily from 14 to 27 February 1985. After 14 days the animals were submitted for necropsy and sections were taken from the application site for microscopic evaluation.

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**TABLE 1 (4)**  
**Evaluation of Skin Reactions**

---

**Erythema and Eschar Formation**

No erythema	0	
Very slight erythema (barely perceptible)	1	
Well-defined erythema	2	
Moderate-to-severe erythema	3	
Severe erythema (beet-redness to slight eschar formation [injurious in depth])	4	
<b>Possible total erythema score</b>		<b>4</b>

**Edema Formation**

No edema	0	
Very slight edema (barely perceptible)	1	
Slight edema (edges of area well-defined by definite raising)	2	
Moderate edema (edges raised approximately 1 mm)	3	
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4	
<b>Possible total edema score</b>		<b>4</b>

<b><u>Possible total score for primary irritation</u></b>		<b>8</b>
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#### Duration of Study

Appendix C is a complete historical listing of study events.

#### Changes/Deviations

This study was conducted in accordance with the protocol and addenda and all applicable SOPs.

#### Storage of Raw Data and Final Report

A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound were retained in the LAIR Archives.

### **RESULTS**

Animals were scored for erythema and edema at each patch site. Three rabbits (85F019, 85F021, 85F024) exhibited very slight erythema (dermal reaction score of 1) at test compound application sites. Three rabbits (85F018, 85F021, 85F024) exhibited very slight erythema (score of 1) at the sham site and two (85F019, 85F021) exhibited very slight erythema (score of 1) at the saline control site. Rabbits 85F019 (compound) and 85F021 (sham) were observed to have very slight erythema 1 hour after dosing. Rabbits 85F018 (sham), 85F021 (compound, sham, vehicle), and 85F024 (compound, sham) exhibited very slight erythema 24 hours after dosing. All rabbits had returned to normal by 48 hours after dosing. Neither edema nor any other recognizable skin reaction was detected at any time during the 14-day observation period. Results of scoring the dermal irritation potential in each rabbit are tabulated in Appendix D.

The quality control animal (85F038) submitted on 25 Jan 85 was unremarkable. Among the 8 rabbits dosed there were no gross pathological lesions attributable to the test compound or test procedures. Histopathological examination of tissues was unremarkable except for the incidental hepatic portal fibrosis in one rabbit (85F018). The Veterinary Pathology Report is presented in Appendix E.

## **DISCUSSION**

The modified Draize dermal irritation test as performed for this study has proven reliable for detecting nonirritating substances and severe irritants but considerably less reliable for detecting mild and moderate irritants (5). Consequently, many systems have been used to score and categorize the dermal irritation potential of a test compound. The system used by the Toxicity Testing Program at LAIR is an adaptation of one used at the U.S. Army Environmental Hygiene Agency (6). It develops a dermal irritation index based on the peak net mean score, which is the maximum net mean score calculated during the 72-hour observation period. Nonirritating compounds have peak net mean scores of 0.0 to 0.5. Mild irritants have peak net mean scores of 0.51 to 2.0. Moderate irritants have peak net mean scores of 2.1 to 5.0. Severe irritants have peak net mean scores of 5.1 to 8.0. Ball Powder® produced very slight erythema in 3 of 8 rabbits. However, each time there was a similiar score at the corresponding vehicle and/or sham sites. Consequently, the peak net mean score was zero. Therefore, Ball Powder® was classified as a nonirritant.

Ball Powder® is insoluble in physiological solutions. In order for a compound to be irritating it must first be absorbed by the skin (7). Most of the Ball Powder® was still present on the skin when the patches were removed, which indicates that the compound was poorly absorbed. This lack of irritation was also observed in a dermal toxicity study performed at this Institute (8).

## **CONCLUSION**

The test compound, Ball Powder®, is not a dermal irritant under conditions of this assay.

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## Appendix A: CHEMICAL DATA

PROPELLANT DESCRIPTION SHEET				REPORTS CONTROL SYMBOL EXEMPT - PARA 7-2e AR 335-15	
TO		FROM Badger Army Ammunition Plant Baraboo, Wisconsin 53913		DATE 10 August 1984	
DA LOT NUMBER 50/50 blend of lots BAJ-47670 and BAJ-47671			COMPOSITION NUMBER WC 844 for Cartridge 5.56 mm, BALL, M193		
MFG AT Badger Army Ammunition Plant			PACKED AMOUNT LB		
CONTRACT NUMBER DAAA09-73-C-0004			SPECIFICATION NUMBER MIL-P-3984E w/Amendment 4 and Drawing No. C10542743 Rev. C		
NITROCELLULOSE					
ACCEPTED BLEND NUMBERS		NITROGEN CONTENT		KI STARCH(65.5°C)	
Nitrocellulose (NC) extracted from excessed Single Base Propellant.		MAX %		MIN	
NC complied with MIL-N-244A		MIN %		MIN	
		AVG %		MIN	
EXPLOSION				HR	
MANUFACTURE OF PROPELLANT					
POUNDS SOLVENT PER POUND NC/DRY WEIGHT INGREDIENTS CONSISTING OF _____ POUNDS ALCOHOL AND _____ POUNDS PER 100 POUNDS SOLVENT. PERCENTAGE REMIX TO WHOLE _____					
TEMPERATURE FROM TO		PROCESS-SOLVENT RECOVERY AND DRYING		TIME DAYS HOURS	
TESTS OF FINISHED PROPELLANT					
PROPELLANT COMPOSITION		TESTS OF FINISHED PROPELLANT		STABILITY AND PHYSICAL TESTS	
CONSTITUENT	% FORMULA	% TOLERANCE	% MEASURED	FORMULA	ACTUAL
Nitroglycerin			10.235	HEAT TEST 120°	Min 60 min 65 min.*
Dinitrotoluene			0.685	No Explosion (HRS)	Min 5 5+*
Diphenylamine			1.105	FORM OF PROPELLANT	
Dibutylphthalate			5.255	Dust & Foreign Mat.	0.02
Nitrocellulose			83.23	Graphite	0.075
Total Volatiles			1.045	Gray Density	1.008
Moisture and Volatiles			0.895	Nitrogen	13.075
Residual Solvent			0.49		
Calcium Carbonate			0.09		
Sodium Sulfate			0.12		
CLOSED BOMB			PROPELLANT DIMENSIONS (INCHES)		
LOT NUMBER	TEMP °F	RELATIVE DENSITY	RELATIVE FORCE	SPEC	DIE
TEST				FINISHED	SPEC
STANDARD		100.00%	100.00%	SPEC	ACTUAL
REMARKS			TEST FINISHED		
			OFFERED		
			DESCRIPTION SHEETS FORWARDED		
TYPE OF PACKING CONTAINER					
REMARKS: *Tested 29 February 1984.					
SIGNATURE OF CONTRACTOR'S REPRESENTATIVE			SIGNATURE OF GOVERNMENT QUALITY ASSURANCE REPRESENTATIVE		

**Appendix B: ANIMAL DATA**

Species: *Oryctolagus cuniculus*

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry  
5265 Starr Way  
Watsonville, CA 95076

Sex: Male and female

Age: Young adults

Animals in each group: 4 males and 4 females

Condition of animals at start of study: Normal

Body weight range at dosing: 3.41 to 4.25 kg

Identification procedures: Ear tag

Pretest conditioning:

1. Quarantine from 25 January - 7 February 1985
2. Animal were close-clipped and examined 24 hours before dosing.

Justification: Laboratory rabbits are a proven sensitive animal model for dermal irritation.

**Appendix C: HISTORICAL LISTING OF STUDY EVENTS**

<u>Date</u>	<u>Event</u>
24 Jan 85	Rabbits arrived at LAIP and were examined and caged.
25 Jan 85	Animals were tattooed, weighed, and placed under a 2-week quarantine. One rabbit (85F038) was submitted to necropsy for quality control.
24 Jan - 7 Feb 85	Animals were checked daily by DACS personnel.
1 Feb 85	Animals were weighed.
7 Feb 85	All rabbits were treated with Canex® and mineral oil in their ears to prevent ear mites. Rabbits were removed from quarantine after being certified healthy by DACS Staff Veterinarian.
8 Feb 85	Animals were weighed.
8 - 12 Feb 85	Animals were checked daily.
12 Feb 85	Animals were close-clipped and areas marked.
13 Feb 85	Animals were weighed. Test substance was applied for 4 hours. Patches were removed and sites scored within 30-60 minutes.
14 - 27 Feb 85	Animals were observed daily.
14 - 16 Feb 85	Areas were scored at 24, 48, and 72 hours after exposure.
20 Feb 85	Animals were weighed.
27 Feb 85	Animals were weighed and submitted for necropsy, skin tissues were collected for microscopic evaluation.

**Appendix D: DERMAL IRRITATION DATA**

<u>ANIMAL NUMBER</u>	<u>OBSERVATION</u>	<u>QUADRANT*</u>			
		<u>I</u>	<u>II</u>	<u>III</u>	<u>IV</u>
85F018	30-60 min	0/0†	0/0	0/0	0/0
	24 hr	1/0	0/0	0/0	0/0
	48 hr#	0/0	0/0	0/0	0/0
85F019	30-60 min	0/0	0/0	1/0	1/0
	24 hr#	0/0	0/0	0/0	0/0
85F020	30-60 min#	0/0	0/0	0/0	0/0
85F021	30-60 min	1/0	0/0	0/0	0/0
	24 hr	1/0	0/0	1/0	1/0
	48 hr#	0/0	0/0	0/0	0/0
85F022	30-60 min#	0/0	0/0	0/0	0/0
85F023	30-60 min#	0/0	0/0	0/0	0/0
85F024	30-60 min	0/0	0/0	0/0	0/0
	24 hr	1/0	1/0	0/0	0/0
	48 hr#	0/0	0/0	0/0	0/0
85F025	30-60 min#	0/0	0/0	0/0	0/0

\* Quadrant I=sham; II, III=treated; IV=saline

† Scores are displayed as erythema/edema

# Scores were 0/0 in all quadrants for remaining observations

**Appendix D (cont.): DERMAL IRRITATION DATA**

## SUMMARY OF PRIMARY IRRITATION TEST DATA

<u>Animal Number</u>	<u>30-60 min</u>			<u>24 h</u>			<u>48 h</u>		
	<u>Test*</u>	<u>Sham</u>	<u>Vehicle</u>	<u>Test</u>	<u>Sham</u>	<u>Vehicle</u>	<u>Test</u>	<u>Sham</u>	<u>Vehicle</u>
85F018	0	0	0	0	1	0	0	0	0
85F019	1	0	1	0	0	0	0	0	0
35F020	0	0	0	0	0	0	0	0	0
85F021	0	1	0	1	1	1	0	0	0
85F022	0	0	0	0	0	0	0	0	0
85F023	0	0	0	0	0	0	0	0	0
85F024	0	0	0	1	1	0	0	0	0
85F025	0	0	0	0	0	0	0	0	0
Mean	0.12	0.12	0.12	0.25	0.38	0.12	0	0	0
Net Mean Score†	0<			0			0		

\*Test value is the larger of the scores in Quadrants II and III.

†Test Mean - (Greater of Sham or Vehicle Mean) = Net Mean Score

<The peak net mean score is 0; therefore, Ball Powder® is a **NON-IRRITANT**

## Appendix E: PATHOLOGY REPORT

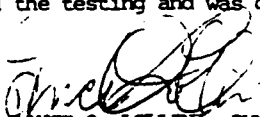
LAIR Pathology Report  
GLP Study 84033  
Primary Dermal Irritation Test in Rabbits (NZW-Albino)  
of Ball Powder (OLIN WC 844)

History: Eight rabbits, 4 each male and female, were tested in accordance with SOP-OP-STX-34 (1 Aug 84). Tissues were submitted for histopathological evaluation.

<u>LAIR Path #</u>	<u>Animal ID #</u>	<u>Sex</u>	<u>Gross Findings</u>	<u>Histologic Findings Skin</u>
36955	85F022	male	NR (not remarkable)	NR
36956	85F023	male	Pinworms - cecum	NR
36957	85F024	male	NR	NR
36958	85F025	male	NR	NR
36959	85F021	female	Pinworms - cecum	NR
36960	85F018	female	Pinworms - cecum, Right lateral lobe liver green*	NR
36961	85F019	female	Pinworms - cecum, 3 mm focal scar, 1 each medial and left lateral liver lobes	NR
36962	85F020	female	Pinworms - cecum	NR

\* Histologic Findings Liver #36960: There were diffuse areas of centrilobular bridging fibrosis throughout the section. Multinucleated cells often containing mineral were present within the fibrous tissue as was hemosiderin. There was piecemeal necrosis of adjacent hepatocytes along some of the borders and a few regions had almost complete loss of liver lobules.

Comments: No lesions were present that were related to the compound tested. The hepatic portal fibrosis seen in animal #85F018 was considered an incidental finding which preceded the testing and was of no consequence.

  
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